REMARKS

Claims 1-30 were pending in the application. Claims 6, 8-10, and 17-30 have been cancelled, without prejudice, as being drawn to a non-elected invention, and claims 1, 3, 7, 11, and 13 have been amended. Accordingly, upon entry of this amendment, claims 1-5, 7, and 11-16 will remain pending. For the Examiner's convenience all of the pending claims, along with the amendments presented herein, are reflected in the listing of claim which begins on page 2 of this paper.

Support for the amendments to the claims may be found throughout the specification, including the originally filed claims. Specifically, support for the amendments to claims 1 and 3 may be found in the originally filed Sequence Listing and the Response filed on May 9, 2002 (Paper No. 19). Support for amendment to claim 11 may be found at least at page 2, lines 2-15; page 3, lines 15-17; page 9, lines 23-33 page 9, lines 29-31; and page 19, lines 1-5 of the specification. Support for amendment to claim 13 may be found in originally filed claim 13.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Election/Restriction

Applicants acknowledge the Examiner's indication that claims 11-12 were incorrectly listed as being directed toward antibodies (versus claims 9-10), which are part of non-elected Group III. Applicants respectfully submit that claims 11-12 are correctly listed herein.

Applicants also acknowledge the Examiner's indication that claims 28-29 are withdrawn as being directed to a nonelected invention.

Allowable Subject Matter

Applicants gratefully acknowledge the Examiner's indication that claims 1 and 2 are allowable.

Oath/Declaration

The Examiner indicates that the oath or declaration is objected to because is lacks the citizenship of the inventors. Applicants are in the process of determining the citenship of the inventors and will forward this information to the Examiner as soon as it is made avaliable.

Drawings

The Office Action indicates that new corrected drawings are required based on the reasons set forth in the Draftsperson's comments in form PTO-948.

Applicants submit herewith corrected drawings, and respectfully request reconsideration and withdrawal of the objection to the drawings.

Rejection of Claims 3-5 and 7 Under 35 U.S.C. §101

Claims 3-5 and 7 have been rejected under 35 U.S.C. §101 because "the claimed invention is directed to non-statutory subject matter." According to the Examiner, the current recitation of "a cell" encompasses a human organism. Although Applicants traverse the foregoing rejection, in an effort to expedite prosecution and in no way conceding the validity of the Examiner's position, Applicants have amended claims 3 and 7 to recite "an isolated host/transfected cell," as suggested by the Examiner. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

Objection to Claim 11

The Examiner has objected to claim 11 for not being incompliance with the Sequence Rules. Accordingly, Applicants have amended the pending claims to recite SEQ ID NOS, thereby, rending the foregoing rejection moot.

Rejection of Claims 11-16 Under 35 U.S.C. §112, First Paragraph

Claims 11, 12, 13, and 14-16 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, "[t]he sole written description provided within the specification is the human hlre1p sequence SEQ ID NO:1 encoding SEQ ID NO:2, (*e.g.*, Figures 8 and 9; pg. 7)....not a single other 'species homologue' of mammalian hlre1p is described; nor is a single 'allelic variant of the polynucleotide' of SEQ ID NO:1 described." The Examiner is further of the opinion that "no written description is provided in the instant specification as to what structurally constitutes broader heterologous encoded 'proteins comprising fragments' thereof...nor can one skilled in the art reasonable visualize or predict what critical encoded amino acid residues would structurally characterize the genus of polynucleotides encoding a 'hlre1p' polypeptide, as currently claimed. In addition, the Examiner is of the opinion that "although the specification describes expression vectors, which can be operably linked to the polynucleotide of SEQ ID NO:1, no generic 'operatively linked...expression control sequence', nor 'hlre1p' promoter sequences, nor other genomic sequences that comprise an 'expression control sequence' are adequately described within the specification that can be visualized by the skilled artisan; thereby also not meeting written description requirements under 35 U.S.C. §112, first paragraph, for claims 12 and 14-16.

Regarding claim 11 and the claims depending therefrom, drawn to species homologues, fragments, and allelic variants of SEQ ID NOS: 1 and 3, Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding species homologues, fragments, and allelic variants to inform a skilled artisan that Applicants were in possession of

the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. 2163.02). The sufficiency of a disclosure in meeting the written description requirement of 35 U.S.C. §112 for claims to a genus of cDNAs was addressed in the Eli Lilly case in which the Court stated that

> [a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus ***or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus*** [*emphasis added*].

The Regents of the University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Therefore, as articulated by the Federal Circuit, a claim to a genus of chemical compounds satisfies the written description requirement when its accompanying specification either defines by sequence a representative number of its members falling within the scope of the genus or ***when its accompanying specification defines the structural features common to a substantial portion of the genus***. The instant specification satisfies this requirement for the claimed invention because the claimed genus of species homologues, fragments, and allelic variants of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. To begin with, the invention provides a novel mammalian bifunctional protein kinase/endoribonuclease referred to herein as hlre1p, as well as a novel cDNA (*hlRE1*) encoding hlre1p. The isolated cDNA is about 3.6 kbp long with an open reading frame extending from nucleotide 97 to 3030, encoding the novel mammalian protein, hlre1p. Indeed, the specification teaches the structure of the hlre1p polypeptide, *i.e.*, the amino acid sequence of the hlre1p polypeptide (SEQ ID NO:2) as well as the structure of the hlre1 nucleic acid molecule, *i.e.*, the nucleotide sequence of the nucleic acid molecule encoding these hlre1p polypeptides (SEQ ID NO:1), and homologues therefore. Moreover, the instant specification teaches that hlre1p is a type 1 transmembrane protein containing a cytoplasmic domain that is highly conserved to the yeast counterpart having a Ser/Thr protein kinase domain and a domain homologous to RNase L; however, the luminal domain has extensively diverged from the yeast gene product. hlre1p expressed in mammalian cells displays intrinsic autophosphorylation activity and an endoribonuclease activity that

cleaves the 5' splice site of yeast *HAC1* mRNA, a substrate for the endoribonuclease activity of yeast Ire1p (page 3, lines 12-17 of the specification).

The specification further teaches at, for example, page 10, lines 10-13, that the invention encompasses allelic variants of the disclosed polynucleotide or protein; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotide. The instant specification also discloses that fragments of the protein of the present invention, which are capable of exhibiting biological activity, are also encompassed by the present invention. Fragments of the protein may, for example, be in linear form or they may be cyclized using known methods, as described in H.U. Saragovi, *et al.*, *BioTechnology* 10:773-778 (1992) and in R.S. McDowell *et al.*, *J. Amer. Chem. Soc.* 114:9245-9253 (1992). Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein-IgM fusion would generate a decavalent form of the protein of the invention (see page 8, lines 23-33; page 9, lines 29-31; page 12, lines 23-32 and page 13, lines 16-21 of the specification).

In summary, Applicants have described a genus of species homologues, fragments, and allelic variants based on structural features that are common to a substantial portion of the genus and have provided within the instant specification the nucleic acid and amino acid sequences of two members of this genus that possess these features. Thus, the instant specification satisfies the written description requirement for the claimed invention, using the standard set forth by the Federal Circuit in The Regents of the University of California.

In view of the foregoing, Applicants respectfully submit that one of skill in the art can readily envision "proteins comprising fragments" of the polypeptide sequence of SEQ ID NO:2, as well as species homologues, fragments, and allelic variants of the hlre1 polypeptides of the present invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing section 112, first paragraph rejection.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 11, 12, 13, and 14-16 have been rejected under 35 U.S.C. §112, first paragraph because the specification while being enabling for an isolated nucleic acid molecule encoding the human hIre1p polypeptide of SEQ ID No:2, does not reasonably provide enablement for any structurally and functionally undefined hIre1p polynucleotides, or biologically functional equivalents thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants respectfully traverse the aforementioned rejection for at least the following reasons. Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed polypeptide molecules to enable one skilled in the art to which it pertains to make and or use the invention.

It is Applicants' position that the claimed genus of the polypeptide molecules of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. In particular, the structure of the claimed genus is taught in the specification, *i.e.*, the sequence of the polypeptide of the invention (SEQ ID NO:2) as well as the structure, *i.e.*, the sequence of the nucleic acid molecules encoding this polypeptide (SEQ ID NO:1). Contrary to the Examiner's assertion, Applicants respectfully submit that the instant specification teaches distinguishing structural features within the claimed genus. For example, hIre1p and yeast Ire1p are both type 1 transmembrane proteins in which the carboxy terminal domains are 34% identical at the amino acid level (see page 7, line 28 through page 8, line 10 of the specification). Although the amino terminal halves of these two proteins have extensively diverged, the amino terminal half of hIre1p is 37% identical to a *C. elegans* putative gene product having a similar domain organization as hIre1p. The cytoplasmic domain of hIre1p contains all the ***conserved*** subdomains present in Ser/Thr protein kinases and a carboxy terminal tail that displays greater homology to human RNase L than *S. cerevisiae* Ire1p. Thus,

based on the teachings in Applicants' specification, one of skill in the art would conclude that Applicants have provided sufficient guidance to enable the claimed invention.

Although Applicants traverse the foregoing rejection, in the interest of expediting prosecution and in no way conceding to the validity of the rejection, Applicants have amended claim 11(c)-(e) to add the phrase "having biological activity." Thus the claimed fragments, species homologues, and allelic variants of the instant invention have biological activity. As set forth below, with respect to the term "biological activity," Applicants respectfully submit that, based on the plain language of this term, one of ordinary skill in the art would understand this term to mean functional, biological activity of the hlre1p protein of the invention.

Accordingly, Applicants submit that the present invention satisfies the requirements of 35 U.S.C. §112, first paragraph.

Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

Claims 11-16 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regards as the invention. Applicants respectfully traverse the foregoing for the following reasons.

Claims 14-16

Claims 14-16 have been rejected because, according to the Examiner, "base claim 13 has been amended to an 'isolated polynucleotide'; thereby no longer providing proper antecedent basis for 'the host cell of claim 13.'"

Applicants respectfully submit that claim 13 has been amended to recite its original claim language. Accordingly, applicants respectfully request withdrawal of the foregoing rejection.

Claims 12 and 16

Claims 12 and 16 have been rejected because, according to the Examiner, it is unclear what is exactly envisioned by the recitation of being "operatively linked to an expression control sequence." In addition, the Examiner alleges that no required vector sequences are recited in claim 11 for expressing "said polypeptide," so that it can be subsequently "expressed", and then "isolated"; thereby, making claim 16 an incomplete method.

Applicants traverse the foregoing rejection. In the present case, Applicants have defined in the specification the term "operatively linked to an expression control sequence" as follows:

> the isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19:4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185:537-566 (1990) (see page 10, lines 15-24 of the specification).

Furthermore, Applicants specifically define the term "operably linked" to mean

> that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/ expression control sequence (see page 10, lines 19-23 of the specification).

Claims 11-16

Claims 11-16 have been rejected because, according to the Examiner, it is unclear what metes and bounds the recitation "having biological activity" is envisioned to entail, in that no specific assayable activity is recited in the claims. Applicants respectfully traverse the foregoing rejection. With respect to the term "biological activity," Applicants respectfully submit that, based on the plain language of this term, one of ordinary skill in the art would understand this term to mean functional, biological activity of the hlre1p protein of the invention. For example,

Applicants teach that expression of *hIRE1* mRNA is autoregulated through a process that requires a functional hIre1p kinase activity. As indicated above, the present specification describes biological activities, including kinase and endonuclease activity, as follows:

> [t]he kinase activity of Ire1p is essential to transmit the UPR signal from the ER to induce specific gene transcription in the nucleus. Mori, K. et al., *Cell* 74:743-756 (1993); Shamu, C.E. et al., *EMBO J.* 15:3028-3039 (1996). Cox and Walter (*J. Biol.Chem.* 264:20602-20607 (1996)) subsequently reported that Ire1p directly regulated biosynthesis of Hac1p, a transcription factor that binds specifically to the UPRE. Recent studies demonstrate that *HAC1* mRNA is synthesized as a precursor that is inefficiently translated. Upon activation of the UPR, Ire1p elicits an endonuclease activity that specifically cleaves an intron from *HAC1* mRNA (see page 2, lines 2-15 of the specification).

The instant specification further teaches biological activity in the form of autophosphorylation activity and an endoribonuclease activity:

> hIre1p expressed in mammalian cells displays intrinsic autophosphorylation activity and an endoribonuclease activity that cleaves the 5' splice site of yeast *HAC1* mRNA, a substrate for the endoribonuclease activity of yeast Ire1p (see page 3, lines 15-17 of the specification).

Furthermore, the instant specification teaches measurement of the functional activity of the kinase.

> The deduced amino acid sequence of hIre1p suggested the presence of an intact catalytic Ser/Thr protein kinase domain. To demonstrate functional activity of the kinase, the capability for autophosphorylation was measured, since this activity correlates with functional activity of yeast Ire1p. Welihinda, A.A. et al., *J. Biol. Chem.* 271:18181-18187 (1996) (see page 19, lines 1-5 of the specification).

In view of the ordinary meaning of these phrases as well as the definitions in Applicants' specification, the skilled artisan would find the term "operatively linked to an expression control sequence" and "having biological activity" to be clear and definite. Accordingly, Applicants respectfully request that the aforementioned rejection be reconsidered and withdrawn.

Rejection of Claims 11-13 and 15-16 under 35 U.S.C. §102(b)

The Examiner has rejected claims 11-13 and 15-16 under 35 U.S.C. §102(b) as being anticipated by Mori *et al.* According to the Examiner, Mori *et al.* teach a polynucleotide encoding an IRE1 protein comprising a fragment of the amino acid sequence of SEQ ID NO:2,

i.e., residue numbers 622-628. Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution, and in no way conceding to the validity of the rejection, claim 11(c) has been amended to specify that the fragment comprises at least 10 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2 having biological activity (see page 9, lines 23-33 and page 9, lines 29-31 of the specification). In view of the amendment to claim 11, the aforementioned rejection has been rendered moot. Accordingly, Applicants respectfully request that the Examiner allow the pending claims.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. UMV-1584 from which the undersigned is authorized to draw.

Dated: October 21, 2003

Respectfully submitted,

By _____

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Attachments